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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,965	12/04/2001	Alain Calvet	5808-01-CA	3513

7590

05/22/2002

Charles W Ashbrook
Warner Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

EXAMINER

DESAI, RITA J

ART UNIT

PAPER NUMBER

1625

DATE MAILED: 05/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

09/980,965

Applicant(s)

CALVET ET AL.

Examiner

RITA J. DESAI

Art Unit

-1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 February 2001.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1-13 in part, drawn to compounds, pharmaceutical composition and a method of use wherein A is a -CH₂- or -C(CH₃)₂ or -CHCH₃- i.e. forms a six membered ring.

Group II, claims 1-13 in part, drawn to compounds, pharmaceutical compositions and a method of treating wherein A is a bond i.e. it forms a five membered ring.

Group III, claims 1-13, drawn to compounds, pharmaceutical compositions and a method of treating wherein A is CH₂CH₂ i.e. it forms a seven membered ring.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

(f) "Markush Practice." The situation involving the so-called "Markush practice" wherein a single claim defines alternatives (chemical or non-chemical) is also governed by Rule 13.2. In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature.

(i) When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

(A) all alternatives have a common property or activity, **and**

(B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives, or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

(ii) In paragraph (f)(i)(B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which

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occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, *the commonly shared structure constitutes a structurally distinctive portion in view of the existing prior art*. The structural element may be a single component or a combination of individual components linked to-gether.

A preliminary search of the core give numerous iterations. See below.

=> s 13

SAMPLE SEARCH INITIATED 14:13:54 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 3170 TO ITERATE

31.5% PROCESSED 1000 ITERATIONS 2 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 60025 TO 66775

This indicates that the core is not novel and that the commonly shared structure does not constitute a distinctive portion in view of the existing prior art.

If applicant 's traverse on the grounds that the inventions are not patentably distinct, applicants should submit evidence or identify such evidence now of record showing the groups to be obvious variants or clearly admit on the record that this is the case. In either instance if the examiner finds one of the inventions unpatentable over the prior art , the evidence or admission may be used in a rejection under 35 USC 103 of the other invention.

During a telephone conversation with Mr. David Kurlandsky on 5/8/2002 a provisional election was made with traverse to prosecute the invention of Group I and a species of example 6 page 25 was elected, claims 1-13 in part drawn to compounds , composition and a method of treating wherein A is -CH₂ or -C(CH₃)₂ or -CHCH₃- i.e. forms a six membered ring. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-13 in part drawn to group II and III are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicants preserve their right to file a divisional on the cancelled non-elected subject matter without prejudice in due course.

This application is being examined to the extent of the elected group wherein A helps form a six membered ring.

Priority

The priority to the provisional application # 60/137,868 is acknowledged.
Also that this is a 371 of PCT/EP00/05783 filed 05/07/2000.

Specification

Abstract

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a *separate* sheet, not more than 25 lines or 250 words including the figure, is required.

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Claim Objections

Claims 3-5, 9-13 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim such as claim 3 cannot further have claims depending upon it. See MPEP § 608.01(n). Accordingly, correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "R1 is an alkyl, alkenyl, or C3-6 cycloalkyl" whereas in claim 1 R1 can only be hydrogen or hydroxy or R1 and R2 together are =O. There is insufficient antecedent basis for this limitation in the claim 1.

(Does applicant mean R5 instead of R1?).

If applicant does mean it to be R1 then the claim is not further limiting but is broader than the Claim 1 and hence improper.

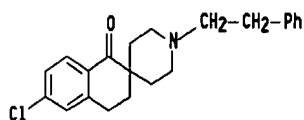
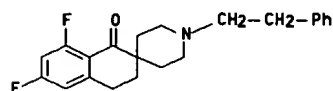
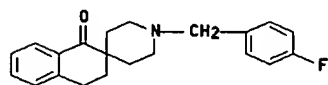
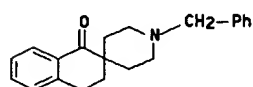
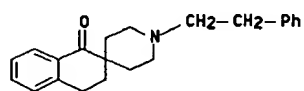
Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-,3,5 ,6 are rejected under 35 U.S.C. 102(b) as being anticipated by Paul Gilligan et al J.Med. Chem. 1994 .

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The Gilligan et al reference discloses the claimed compounds . See compound 14 on page 365 and table 2 page 366 of the reference.



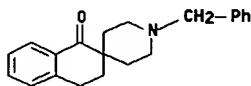
The above compounds read on the compounds of the invention when its R₁ and R₂ together form a =O, R₃ and R₄ may be a hydrogen or a halogen, A is a CH₂ and R₅ is alkyl substituted by a phenyl or a substituted phenyl.

The reference also discloses that the compound 14 was superior in *in vivo* activity than the isomeric tetralins of formula 5b and 5c on page 364.

Claims 1-3,5-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilma Quaglia et al 1'-Benzyl-3,4-dihydrospiro[2H-1-benzothiopyran-2,4'-piperidine], a potent and highly selective signal ligand.

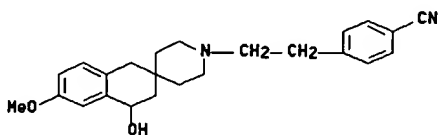
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The reference discloses the spirotetralin 1 which are potent sigma ligands. See formula 1 on page 1557 of the reference. See compound 1 in table 1 on page 1559.



Claim 1-5 (claim 4 is included with the assumption that applicant means R1 to be R5) are rejected under 35 U.S.C. 102(b) as being anticipated by Claremon et al US 5439914.

The reference discloses the compounds wherein R1 or R2 is H and then the other is an OH and R5 would be an alkyl substituted by a substituted phenyl R4 is a hydrogen and R3 is an alkoxy (methoxy).



Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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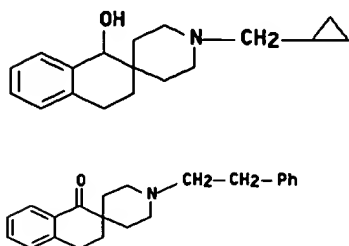
The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

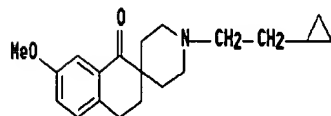
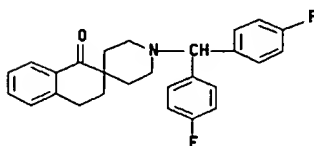
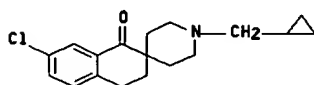
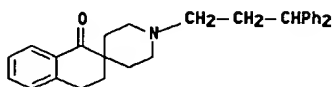
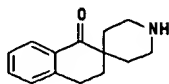
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Piperidinyltetralin sigma ligands Gilligan et al in combination with EP 414 289 Billington et al and Journal of Clinical Anesthesia Laszlo Gyermek.

The instant application is drawn to a spiro tetralin of the following structure.



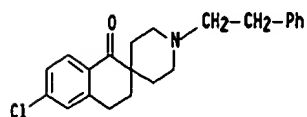
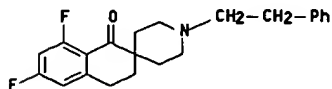
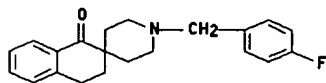
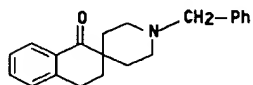
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These compounds are used in a pharmaceutical composition to treat various types of pain.

Scope and Content of Prior Art MPEP 2141.01

Gilligan discloses compounds as given below.

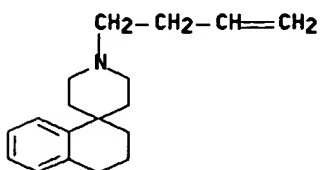
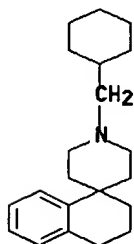
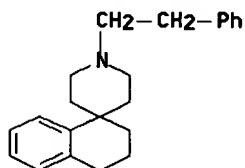
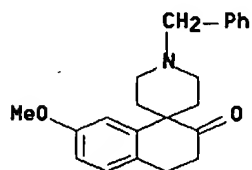
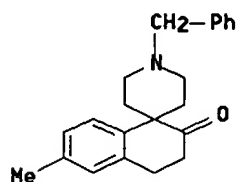


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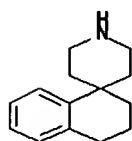
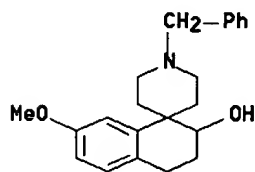
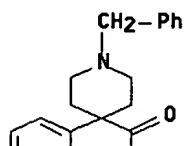
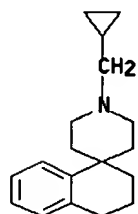
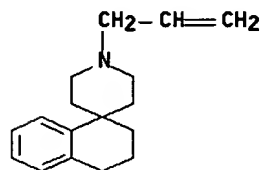
and other tetralins (which are included in the Billington EP'289 reference) which are agonists of serotonin 5HT2 receptor and sigma 1.

It also discloses that the compound 14 had superior in vivo activity towards serotonin (5HT2 receptor) than the isomeric tetralins of formula 5a, 5b and 5c See on page 365 second column.

Billington et al EP 414289 discloses compounds of the formula



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See claim 12 and the examples in the reference.

Journal of Clinical Anesthesia Laszlo Gyermek in its article teaches that serotonin (5-hydroxytryptamine) is envisioned in the treatment of certain types of pain syndromes.

Difference Between the Prior Art and the Claims MPEP 2141.02

Gilligan discloses only some of the substituents on its spiro tetralin compound.

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Billington et al discloses the isomeric tetralin but with some of the same substituents of the application, such as the cyclo groups

Prima Facie Obviousness Rational and Motivation MPEP 2142-2143

Gilligan clearly teaches that the tetralin compounds are more potent than the its isomers of the same core as the Billington compounds. The reference discloses that the compound 14 (Gilligan compound) had superior in vivo activity than the isomeric tetralins of formula 5a, 5b and 5c (Billington compounds) on page 364.

Thus motivating a person of ordinary skill in the art such as a chemist or a pharmacist to make the spiral tetralin compounds of Gilligan rather than its Billington analogs.

Journal of Clinical Anesthesia Laszlo Gyermek in its article teaches that serotonin (5-hydroxytryptamine) is envisioned in the treatment of certain types of pain syndromes.

Thus one of skill in the art would have found it Prima Facie Obvious to modify the compounds of Billington by making the tetralin spiro isomeric structure similar to the ones found in Gilligan and use them for treating various types of pain disorders.

Conclusion

Thus the claims 1-13 are not found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RITA J. DESAI whose telephone number is 703-305-1868. The examiner can normally be reached on Monday - Friday, 9:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Alan Rotman can be reached on 703-308-4698. The fax phone numbers for the

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organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-7922 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

A handwritten signature in cursive script, appearing to read "R.D. Desai", with a horizontal line drawn underneath the name.

R.D.

May 17, 2002